

CLAIMS

We claim:

1. A targeting construct comprising:

- (a) a first polynucleotide sequence homologous to a target gene, wherein the target gene is a magnesium-dependent protein phosphatase gene,
- (c) a second polynucleotide sequence homologous to the target gene; and
- (d) a selectable marker.

2. The targeting construct of claim 1, wherein the targeting construct further comprises a screening marker.

10 3. A method of producing a targeting construct, the method comprising:

- (a) obtaining a first polynucleotide sequence homologous to a magnesium dependent protein phosphatase gene;
- (b) obtaining a second polynucleotide sequence homologous to a magnesium dependent protein phosphatase gene;
- (c) providing a vector comprising a selectable marker; and
- (d) inserting the first and second sequences into the vector, to produce the targeting construct.

4. A method of producing a targeting construct, the method comprising:

- (a) providing a polynucleotide sequence homologous to a magnesium-dependent protein phosphatase;
- (b) generating two different fragments of the polynucleotide sequence;
- (c) providing a vector having a gene encoding a selectable marker; and
- (d) inserting the two different fragments into the vector to form the targeting construct.

25 5. A cell comprising a disruption in a magnesium-dependent protein phosphatase gene.

6. The cell of claim 5, wherein the cell is a murine cell.

7. The cell of claim 6, wherein the murine cell is an embryonic stem cell.

8. A non-human transgenic animal comprising a disruption in a magnesium-dependent protein phosphatase.

30 9. A cell derived from the non-human transgenic animal of claim 8.

10. A method of producing a transgenic mouse comprising a disruption in a magnesium-dependent protein phosphatase gene, the method comprising:

- (a) introducing the targeting construct of claim 1 into a cell;
- (b) introducing the cell into a blastocyst;
- (c) implanting the resulting blastocyst into a pseudopregnant mouse, wherein said pseudopregnant mouse gives birth to a chimeric mouse; and
- (d) breeding the chimeric mouse to produce the transgenic mouse.

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11. A method of identifying an agent that modulates the expression of a magnesium-dependent protein phosphatase, the method comprising:

- 10 (a) providing a non-human transgenic animal comprising a disruption in a magnesium-dependent protein phosphatase gene;
- (b) administering an agent to the non-human transgenic animal; and
- (c) determining whether the expression of magnesium-dependent protein phosphatase in the non-human transgenic animal is modulated.

15 12. A method of identifying an agent that modulates the function of a magnesium-dependent protein phosphatase, the method comprising:

- (a) providing a non-human transgenic animal comprising a disruption in a magnesium-dependent protein phosphatase gene;
- (b) administering an agent to the non-human transgenic animal; and
- 20 (c) determining whether the function of the disrupted magnesium-dependent protein phosphatase gene in the non-human transgenic animal is modulated.

13. A method of identifying an agent that modulates the expression of magnesium-dependent protein phosphatase, the method comprising:

- 25 (a) providing a cell comprising a disruption in a magnesium-dependent protein phosphatase gene;
- (b) contacting the cell with an agent; and
- (b) determining whether expression of the magnesium-dependent protein phosphatase is modulated.

14. A method of identifying an agent that modulates the function of a magnesium-dependent protein phosphatase gene, the method comprising:

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(a) providing a cell comprising a disruption in a magnesium-dependent protein phosphatase gene;

(b) contacting the cell with an agent; and

(c) determining whether the function of the magnesium-dependent protein phosphatase gene is modulated.

15. The method of claim 13 or claim 14, wherein the cell is derived from the non-human transgenic animal of claim 8.

16. An agent identified by the method of claim 11, claim 12, claim 13, or claim 14.

17. A transgenic mouse comprising a disruption in a magnesium-dependent protein phosphatase gene, wherein the transgenic mouse exhibits a lung abnormality or an elevated white blood cell count.

18. The transgenic mouse of claim 17, wherein the lung abnormality comprises pulmonary lesions.

19. The transgenic mouse of claim 18, wherein the pulmonary lesions are consistent with pneumonia.

20. The transgenic mouse of claim 17, wherein the transgenic mouse is heterozygous for a disruption in a magnesium-dependent protein phosphatase gene.

21. The transgenic mouse of claim 17, wherein the transgenic mouse is homozygous for a disruption in a magnesium-dependent protein phosphatase gene.

22. A method of producing a transgenic mouse comprising a disruption in a magnesium-dependent protein phosphatase gene, wherein the transgenic mouse exhibits a lung abnormality or an elevated white blood cell count, the method comprising:

(a) introducing a magnesium-dependent protein phosphatase gene targeting construct into a cell;

(b) introducing the cell into a blastocyst;

(c) implanting the resulting blastocyst into a pseudopregnant mouse, wherein said pseudopregnant mouse gives birth to a chimeric mouse; and

(d) breeding the chimeric mouse to produce the transgenic mouse comprising a disruption in a magnesium-dependent protein phosphatase gene.

23. A cell derived from the transgenic mouse of claim 17 or claim 22, wherein the cell comprises a disruption in a magnesium-dependent protein phosphatase gene.

24. A method of identifying an agent that ameliorates a lung abnormality, the method comprising:

- (a) administering an agent to a transgenic mouse comprising a disruption in a magnesium-dependent protein phosphatase gene; and
- 5 (b) determining whether the agent ameliorates the lung abnormality of the transgenic mouse.

25. The method of claim 24, wherein the lung abnormality comprises pulmonary lesions.

26. The method of claim 25, wherein the pulmonary lesions are consistent with pneumonia.

10 27. A method of identifying an agent that reduces white blood cell count, the method comprising:

- (a) administering an agent to a transgenic mouse comprising a disruption in a magnesium-dependent protein phosphatase gene; and
- 15 (b) determining whether the agent reduces white blood cell count in the transgenic mouse.

28. A method of identifying an agent which modulates magnesium-dependent protein phosphatase gene expression, the method comprising:

- (a) administering an agent to the transgenic mouse comprising a disruption in a magnesium-dependent protein phosphatase gene; and
- 20 (b) determining whether the agent modulates magnesium-dependent protein phosphatase gene expression in the transgenic mouse, wherein the agent modulates a phenotype associated with a disruption in a magnesium-dependent protein phosphatase gene.

25 29. The method of claim 28, wherein the phenotype comprises a lung abnormality or an elevated white blood cell count.

30. The method of claim 29, wherein the lung abnormality comprises pulmonary lesions.

31. The method of claim 30, wherein the pulmonary lesions are consistent with pneumonia.

30 32. A method of identifying an agent which modulates a phenotype associated with a disruption in a magnesium-dependent protein phosphatase gene, the method comprising:

(a) administering an agent to a transgenic mouse comprising a disruption in a magnesium-dependent protein phosphatase gene; and

(b) determining whether the agent modulates the phenotype.

5 33. The method of claim 32, wherein the phenotype comprises a lung abnormality or an elevated white blood cell count.

34. The method of claim 33, wherein the lung abnormality comprises pulmonary lesions.

35. The method of claim 34, wherein the pulmonary lesions are consistent with pneumonia.

10 36. A method of identifying an agent which modulates magnesium-dependent protein phosphatase gene expression, the method comprising:

(a) providing a cell comprising a disruption in a magnesium-dependent protein phosphatase gene;

(b) contacting the cell with an agent; and

15 (c) determining whether the agent modulates magnesium-dependent protein phosphatase gene expression, wherein the agent modulates a phenotype associated with a disruption in a magnesium-dependent protein phosphatase gene.

37. The method of claim 36, wherein the phenotype comprises a lung abnormality or an elevated white blood cell count.

38. The method of claim 37, wherein the lung abnormality comprises pulmonary lesions.

20 39. The method of claim 38, wherein the pulmonary lesions are consistent with pneumonia.

40. A method of identifying an agent which modulates magnesium-dependent protein phosphatase gene function, the method comprising:

25 (a) providing a cell comprising a disruption in a magnesium-dependent protein phosphatase gene;

(b) contacting the cell with an agent; and

(c) determining whether the agent modulates magnesium-dependent protein phosphatase gene function,

30 (d) a phenotype associated with a disruption in a magnesium-dependent protein phosphatase gene.

41. The method of claim 40, wherein the phenotype comprises a lung abnormality or an elevated white blood cell count.

42. The method of claim 41, wherein the lung abnormality comprises pulmonary lesions.

43. The method of claim 42, wherein the pulmonary lesions are consistent with pneumonia.

44. An agent identified by the method of claim 24, claim 27, claim 28, claim 32, claim 36, or claim 40.

45. A transgenic mouse comprising a disruption in a magnesium-dependent protein phosphatase gene, wherein the transgenic mouse exhibits increased anxiety.

46. The transgenic mouse of claim 45, wherein the transgenic mice demonstrates a decrease in time spent in the central region of the open field test.

47. A transgenic mouse comprising a disruption in a magnesium-dependent protein phosphatase gene, wherein the transgenic mouse exhibits an increased pain threshold.

48. The transgenic mouse of claim 45 or claim 47, wherein the transgenic mouse is heterozygous for a disruption in a magnesium-dependent protein phosphatase gene.

49. The transgenic mouse of claim 45 or claim 47, wherein the transgenic mouse is homozygous for a disruption in a magnesium-dependent protein phosphatase gene.

50. A method of producing a transgenic mouse comprising a disruption in a magnesium-dependent protein phosphatase gene, wherein the transgenic mouse exhibits increased anxiety, the method comprising:

(a) introducing a magnesium-dependent protein phosphatase gene targeting construct into a cell;

(b) introducing the cell into a blastocyst;

(c) implanting the resulting blastocyst into a pseudopregnant mouse, wherein said pseudopregnant mouse gives birth to a chimeric mouse; and

(d) breeding the chimeric mouse to produce the transgenic mouse comprising a disruption in a magnesium-dependent protein phosphatase gene.

51. A method of producing a transgenic mouse comprising a disruption in a magnesium-dependent protein phosphatase gene, wherein the transgenic mouse exhibits increased pain threshold, the method comprising:

- (a) introducing a magnesium-dependent protein phosphatase gene targeting construct into a cell;
- (b) introducing the cell into a blastocyst;
- (c) implanting the resulting blastocyst into a pseudopregnant mouse, wherein said pseudopregnant mouse gives birth to a chimeric mouse; and
- (d) breeding the chimeric mouse to produce the transgenic mouse comprising a disruption in a magnesium-dependent protein phosphatase gene.

52. A cell derived from the transgenic mouse of claim 45, claim 47, claim 50 or claim 51, wherein the cell comprises a disruption in a magnesium-dependent protein phosphatase gene.

53. A method of identifying an agent that ameliorates increased anxiety, the method comprising:

- (a) administering an agent to a transgenic mouse comprising a disruption in a magnesium-dependent protein phosphatase gene; and
- (b) determining whether the agent ameliorates anxiety of the transgenic mouse.

54. A method of identifying an agent which modulates a phenotype associated with a disruption in a magnesium-dependent protein phosphatase gene, the method comprising:

- (a) administering an agent to a transgenic mouse comprising a disruption in a magnesium-dependent protein phosphatase gene; and
- (b) determining whether the agent modulates anxiety.

55. A method of identifying an agent which modulates magnesium-dependent protein phosphatase gene function, the method comprising:

- (a) administering an agent to a transgenic mouse comprising a disruption in a magnesium-dependent protein phosphatase gene;
- (b) determining whether the agent modulates magnesium-dependent protein phosphatase gene function, wherein the agent modulates anxiety.

56. An agent identified by the method of claim 53, claim 54, or claim 55.

57. A method of treating anxiety, the method comprising administering to a subject in need, a therapeutically effective amount of an agent that modulates the expression or activity of a magnesium-dependent protein phosphatase.

58. The method of claim 57, wherein the agent is an agonist to a magnesium-dependent protein phosphatase.

59. A method of treating anxiety, the method comprising administering to a subject in need a therapeutically effective amount of a magnesium-dependent protein phosphatase.

5 60. The method of claim 59, wherein the magnesium-dependent protein phosphatase is encoded by a magnesium-dependent protein phosphatase gene.

61. The method of claim 60, wherein the magnesium-dependent protein phosphatase gene is comprised of SEQ ID NO:1.

10 62. A pharmaceutical composition comprising a magnesium-dependent protein phosphatase.

63. A method of treating anxiety, the method comprising administering to a subject in need a therapeutically effective amount of a magnesium-dependent protein phosphatase.

64. The method of claim 59, wherein the magnesium-dependent protein phosphatase is encoded by a magnesium-dependent protein phosphatase gene.

15 65. The method of claim 60, wherein the magnesium-dependent protein phosphatase gene is comprised of SEQ ID NO:1.

66. A pharmaceutical composition comprising a magnesium-dependent protein phosphatase.

20 67. A method of reducing pain, the method comprising administering to a subject in need, a therapeutically effective amount of an agent that modulates the expression or activity of a magnesium-dependent protein phosphatase.

68. The method of claim 67, wherein the agent inhibits or reduces the expression or activity of a magnesium-dependent protein phosphatase.

25 69. A method of identifying an agent that ameliorates or reduces pain, the method comprising:

(a) administering an agent to a transgenic mouse comprising a disruption in a magnesium-dependent protein phosphatase gene; and

(b) determining whether the agent ameliorates or reduces pain in the transgenic mouse.

30 70. A method of identifying an agent which modulates a phenotype associated with a disruption in a magnesium-dependent protein phosphatase gene, the method comprising:

(a) administering an agent to a transgenic mouse comprising a disruption in a magnesium-dependent protein phosphatase gene; and

(b) determining whether the agent modulates pain in the transgenic mouse.

71. A method of identifying an agent which modulates magnesium-dependent protein phosphatase gene function, the method comprising:

(a) administering an agent to a transgenic mouse comprising a disruption in a magnesium-dependent protein phosphatase gene;

(b) determining whether the agent modulates magnesium-dependent protein phosphatase gene function, wherein the agent alleviates or reduces pain in the transgenic mouse.

72. An agent identified by the methods of claim 69, claim 70, or claim 71.